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# Effect of concurrent intramuscular administration of Meloxicam on the Pharmacokinetics of Cefquinome in Goats

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## Abstract

The deposition kinetics of Cefquinome (2mg/kg) was studied following intramuscular administration of it alone and co-administered with meloxicam (0.2 mg/kg) in goats. The concentration of Cefquinome in serum was detected by HPLC. Following single dose intramuscular administration of Cefquinome alone, peak plasma concentration (1.71±0.0189µg/mL) was obtained at 1.59±0.0038 h. The absorption half-life ($t_{1/2ab}$), total body clearance ($Cl_{tot}$), elimination half-life ($t_{1/2el}$) and area under curve ($AUC_{(0\text{-}inf)}$) of Cefquinome were 0.4±0.0028h, 0.068±0.78L/h/kg, 9.21±0.178 h and 29.36±0.78µg.h.ml$^{-1}$, respectively. No significant changes were reported in the pharmacokinetic parameters following co-administration of Cefquinome with meloxicam. Following single dose intramuscular co-administration of Cefquinome and meloxicam, peak plasma concentration (1.60±0.0124µg/mL) was obtained at 1.49±0.0092h. The absorption half-life ($t_{1/2ab}$), total body clearance ($Cl_{tot}$), elimination half-life ($t_{1/2el}$) and area under curve ($AUC_{(0\text{-}inf)}$) of Cefquinome were 0.396±0.006 h, 0.094±0.25 L/h/kg, 6.5±0.221hand 21.38±0.696µg.h.ml$^{-1}$, respectively. From our results, may be concluded that intramuscular administration of meloxicam (0.2 mg/kg) may be successfully co-administrated with Cefquinome (2 mg/kg) for combating bacterial infections with an inflammatory condition in goats without any antagonistic effect.

**Keywords:** Kinetic, Cefquinome, meloxicam, intramuscular, goats.

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## 1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and antimicrobials are commonly prescribed together for the treatment of infectious diseases in goats [1,2].

Cefquinome is a β-lactam antibiotic of the cephalosporin class (a fourth generation cephalosporin). It has a broad spectrum of activity against both gram-positive and gram-negative bacteria, including *Actinobacillus pleuropneumoniae*, *Haemophilus spp., Actino bacillus spp.*, *Coryne bacterium, Erysipelothrix rhusiopathiae, Clostridium spp., Streptococcus spp*. and *Pasteurella spp.*

The shape of the Cefquinome molecule tends to facilitate distribution in treated animals and passage through bacterial cell walls, resulting in rapid bactericidal effect by inhibition to cell wall formation. It also increased resistant against inactivation by bacteria that produce β-lactamase enzyme; those studies were mentioned by Hwang *et al* [3], & Tiwari *et al* [2].

Fourth-generation cephalosporins are zwitterions that can penetrate the outer membrane of Gram-negative bacteria. They also have a greater resistance to β-lactamases than the third-generation cephalosporins. Many can cross the blood–brain barrier and are effective in meningitis [4].

Meloxicam is a member of the oxicam group of NSAIDs whose mode of action may be related to inhibition of COX enzyme and it has anti-inflammatory, analgesic and antipyretic activities [5].

Taking into consideration the above facts, this study was done in order to investigate pharmacokinetic parameters of Cefquinome alone and co-administration between Cefquinome and meloxicam after intramuscular injection in goats.

## 2. Material and methods

### 2.1. Drugs

**Cefquinome**:

It was obtained from Intervet International Company, Cairo, Egypt, under a trade name of (Cobactan 2.5%).

**Meloxicam:**

It was obtained from Medical Union Pharmaceuticals (MUP) company, Egypt as Injectable solution under a trade name of (Mobitil15mg/1.5ml Ampoule).

### 2.2. Animals

The experiment was performed on five Egyptian Baladi goats of 1-2 years of age and weighing between 15 - 22kg. The animals were housed in separate pens and provided standard ration with *ad libitum* water. Goats were kept under constant observation for two weeks before the experiment and subjected to clinical examination to exclude the possibility of any diseases. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Sadat city University, Egypt.

### 2.3. Experimental design

Each goat was injected intramuscularly at the dose rate of 2mg/kg b.wt. Cefquinome (Cobactan 2.5%) into the deep gluteal muscle of hindquarter alone and then after fifteen days washout period, these animals also injected intramuscularly at the dose rate of 2mg/kg b.wt. Cefquinome [6,7] along with meloxicam at the dose rate of 0.2mg/kg b.wt. as dose mentioned by Tiwari *et al* [2].

### 2.4. Blood samples

Blood samples (2 mL) were collected after intramuscular injection of Cefquinome alone at (0.083, 0.25, 0.5, 1,2, 4, 6, 8, 12 and 24 h post administration and after concurrent intramuscular injection of Cefquinome (2mg/kg b.wt.) and meloxicam (0.2mg/kg b.wt.) at (0.083,0.25,0.5,1,2, 4, 6, 8, 12 and 24 h post administration. All blood samples were left to clot for 30 min., centrifuged at 3000 rpm for 15 min. and the obtained clear sera were transferred to eppendorf's tubes and kept at -20$^0$C. Samples were analyzed to quantify Cefquinome concentration using HPLC.

### 2.5. Analytical analysis

Serum concentrations of Cefquinome were determined using a high performance liquid chromatographic (HPLC) method. Sample analysis, solutions and HPLC conditions were carried out according to Lina [8].

0.5 ml of serum or supernatant of tissues was added to 3 ml of Acetonitrile in centrifugation tubes and was mixed for 1 min by vortex, samples was centrifuged at 3000 rpm for 20 min, then the supernatant was transferred to other centrifuge tube and was evaporated under nitrogen flow to dryness, then 150 µl of mobile phase and 400 µl of Hexane was added to dry sample and mixed for 1 min by vortex, samples were centrifuged at 3000 rpm for 20 min, the supernatant was discarded and 50 µl was injected to HPLC[9].

### 2.6. Pharmacokinetic analysis

Serum concentrations of Cefquinome versus time curve were generated, and best fitted by the aid of computer poly-exponential curve stripping program, (RStrip Micromath, software, USA). Data from each goat was fitted individually and the pharmacokinetic variables were computed by the aid of the software programs. The hybrid rate constants of the distribution and elimination phase (α and β), the first order absorption and elimination rate constants ($K_{ab}$ and $K_{el}$),corresponding extrapolated zero time intercepts (A and B), absorption, distribution & elimination half lives ($t_{0.5ab}$, $t_{0.5\alpha}$, $t_{0.5\beta}$, $t_{0.5el}$), transfer rate constants($K_{12}$ and $K_{21}$), the area under the curve from zero to infinite time (AUC0-∞), mean residence time (MRT),maximum serum concentration ($C_{max}$) and time to be achieved ($T_{max}$) were calculated. The other pharmacokinetic parameters as total body clearance, the volume of the central compartment ($V_c$), the volume ofdistribution at steady state ($V_{dss}$) were calculated according to Baggot [10]. The results were expressed as mean±SE and theobtained data statistically using Student ”t” test asdescribed by Snedecor [11].

## 3. Results

### 3.1. Single intramuscular administration of Cefquinome alone

The serum Cefquinome concentrations following its single intramuscular administration of 2mg/kg b.wt.bwere recorded in table (1) and figure (1). Cefquinome was firstly detected in serum 10 minutes following its intramuscular administration with a mean value of (0.95 ± 0.11µg/ml). The mean peak serum level (1.96±0.026µg/ml) achieved 2 hour post intramuscular administration. The drug was still detected in a concentration of (0.53 ±0.017µg/ml) at 24 hours in serum of goats.

The pharmacokinetic parameters of Cefquinome following intramuscular administration of 2mg/kg b.wt. were recorded in table 2.

The results revealed that, Cefquinome was rapidly absorbed after its intramuscular administration with an absorption rate constant ($k_{ab}$) of 1.75±0.012 $h^{-1}$ and the calculated value for $t_{0.5ab}$ was found to be 0.4±0.0028 h.

The maximum serum concentration ($C_{max}$) was found to be 1.71±0.0189 µg/ml reached at 1.59±0.0038h. post intramuscular administration. The elimination half-life ($t_{0.5el}$) was 9.21±0.178 h., the mean residence time (MRT) was 13.63±0.254h., the calculated AUC (0-inf) was found

to be 29.36±0.78 µg.h.ml$^{-1}$. The calculated interval between doses (IBD) was found to be 36.15±0.25h and total body clearance was 0.068± 0.78 L/h/kg.

### 3.2. Single intramuscular Co-administration of Cefquinome and meloxicam

The serum Cefquinome concentrations after a single intramuscular administration of 2mg/kg b.wt.in goats pretreated with meloxicam were recorded in table (1) and figure (1). The mean peak serum level (1.81± 0.014µg/ml) was achieved 2 hour post administration. The drug was still detected in a concentration of 0.38±0.019µg/ml at 24 hours post administration in serum of meloxicam pretreated goats.

The pharmacokinetic parameters of Cefquinome following a single intramuscular administration of 2mg/kg b.wt.in goats pretreated with meloxicam were recorded in table (2). The results revealed that Cefquinome was rapidly absorbed post intramuscular administration with an absorption rate constant ($k_{ab}$) of 1.82±0.036 h$^{-1}$.

The maximum serum concentration ($C_{max}$) of 1.6 ± 0.0124 µg/ml was reach at 1.49 ± 0.0092 h.The elimination half-life ($t_{0.5el}$) was 6.5±0.221h. The mean residence time (MRT) was 9.77±0.309 h. The AUC $_{(0\text{-inf})}$ was found to be21.38± 0.696 µg.h.ml$^{-1}$. The calculated interval between doses (IBD) was found to be 24.56± 0.27hours andtotal body clearance was 0.094± 0.25L/h/kg.

**Table 1:** Mean serum concentration (µg/ml) of Cefquinomein goats after a single IM administration of 2 mg/kg b.wt. alone (Cef. I.M.) and /or pretreated with meloxicam (Cef.I.M+melox) intramuscular at a dose rate of 0.2mg/kg b.wt.(n= 5).

| Time( h) | Groups ( X ± S.E.) | |
|---|---|---|
| | ***Cef. I.M*** | ***Cef.I.M+melox.*** |
| 0.083 | 0.95 ± 0.011 | 0.75 ± 0.018 |
| 0.25 | 1.21 ±0.011 | 1.05 ±0.019 |
| 0.5 | 1.32 ±0.015 | 1.24 ±0.018 |
| 1 | 1.65 ± 0.0181 | 1.52 ± 0.017 |
| 2 | 1.96 ±0.026 | 1.81 ± 0.014 |
| 4 | 1.31 ±0.015 | 1.12 ± 0.018 |
| 8 | 0.98 ±0.0195 | 0.75 ±0.021 |
| 12 | 0.79 ± 0.018 | 0.58 ± 0.014 |
| 24 | 0.53 ± 0.017 | 0.38 ± 0.019 |

**Table 2:** Mean pharmacokinetic parameters of cefquinome in goats after a single IM administration of 2 mg/kg b.wt. alone (Cef. I.M.) and /or pretreated with meloxicam (Cef. I.M. + Melox.) IM at a dose rate of 0.2 mg/kgb.wt.(n= 5).

| Parameter | Units | X ± S.E. | |
|---|---|---|---|
| | | **Cef. I.M.** | **Cef. I.M. + Melox** |
| A | µg.ml$^{-1}$ | 1.23 ±0.0102 | 1.432 ± 0.017 |
| $K_{ab}$ | h$^{-1}$ | 1.75 ± 0.012 | 1.82 ± 0.036 |
| $T_{0.5(ab)}$ | h | 0.4 ±0.0028 | 0.396 ± 0.006 |
| B | µg.ml$^{-1}$ | 2.01 ±0.017 | 1.98±0.0139 |
| $K_{el}$ | h$^{-1}$ | 0.075 ±0.0015 | 0.11 ± 0.003 |
| $T_{0.5(el)}$ | h | 9.21 ± 0.178 | 6.5 ±0.221** |
| $C_{max}$ | µg.ml$^{-1}$ | 1.71 ± 0.0189 | 1.6 ± 0.0124 |
| $T_{max}$ | h | 1.59 ± 0.0038 | 1.49 ± 0.0092 |
| $AUC_{(0\text{-inf})}$ | µg.h.ml$^{-1}$ | 29.36 ± 0.78 | 21.38 ± 0.696** |
| MRT | h | 13.63 ± 0.254 | 9.77 ± 0.309** |
| IBD | h | 36.15± 0.25 | 24.56± 0.27** |
| $Cl_{tot}$ | L/h/kg | 0.068± 0.78 | 0.094± 0.25 |

*** **p ≤ 0.001** ** **p ≤ 0.01** * **p ≤ 0.05**

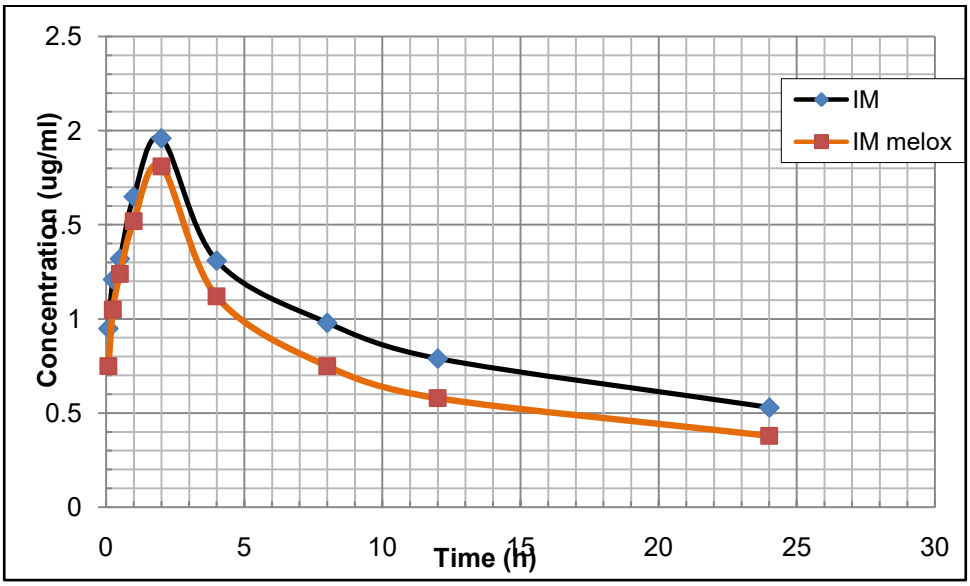


**Figure 1: Graph depicting the time course of Cefquinome in serum of goats after a single intramuscular dose of 2 mg/kgb.wt. alone (IM) and co-administration with meloxicam (IM + Melox).**

## 4. Discussion

In the present study, following intramuscular administration of Cefquinome with meloxicam, a significant decrease in elimination half-life ($t_{½el}$) (6.5±0.221 h), $AUC_{(0\text{-}inf)}$ (21.38±0.696) and MRT (9.77±0.309) was observed. Whereas all other pharmacokinetic parameters were not significantly altered as compared to Cefquinome only.

A non-significant difference was in peak plasma concentration ($C_{max}$) of Cefquinome alone or co-administrated with meloxicam in goats (1.71±0.0189&1.60±0.024µg/mL), respectively as compared. Similarly to that reported by Patel *et al* [12] whose mentioned that there were non-significant differences in the $C_{max}$ of cefepime following concomitant intramuscular administration ofketoprofen in goats.

In the present study, following intramuscular administration of Cefquinome with meloxicam in goats; the major pharmacokinetics parameters were not significantlyaltered in comparison to goats administered Cefquinome alone. Similarly, the majorpharmacokinetic parameters of cefmenoxime remained unaffected following concomitantdiclofenac sodium administration in rabbits [13] which supports the results of our study. No significant alterations were found in the major pharmacokinetic parametersof cefepime following its concomitant intramuscular administration with ketoprofenin sheep [14], which is in agreement with the present study. And also similar to that reported by Rana *et al* [1] whose stated thatfollowing intramuscular administration of Cefquinome withtolfenamic acid in sheep, the major pharmacokinetics parameters were not significantlyaltered in comparison to sheep administered Cefquinome alone.

In contrast to the present study, Barot [15] reported a significant increase in the $C_{max}$ of cefpirome following co-administration of it with ketoprofen in goats and Tiwari *et al* [2] stated a significant increase in the major parameters of Cefquinome following co-administration with meloxicam in goats when compared with Cefquinome only. Reports of alterations in the pharmacokinetic parameters of cephalosporin when co-administered with NSAIDs may be due to differences in the species of animal and the chemical nature of the drugs.

The results of our study showed that non-significant changes in the major pharmacokinetic parameters of Cefquinome were observed following its concomitant administration with meloxicam in goats. So, it may be concluded that intramuscular administration of meloxicam (0.2 mg/kg) may be successfully co-administrated with Cefquinome (2 mg/kg) for combating bacterial infections with an inflammatory condition in goats without antagonistic effect.

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